3. TOXICITY REFERENCE VALUES FOR SUBSTITUTES

To assess potential health risks from exposure to substitutes for ozone-depleting substances (ODSs) in the aerosols sector, EPA identified or developed toxicity reference values for each substitute. These values include occupational exposure limits, reference concentrations, and cancer slope factors. The toxicity reference values were compared to or combined with predicted exposure concentrations to estimate risks to workers and the general population, as described in subsequent chapters of this report.

This chapter first discusses EPA's general approach for identifying or developing the toxicity reference values for substitutes examined in the SNAP background documents. Section 3.1 discusses occupational exposure limits, and Section 3.2 discusses general population toxicity reference values. Both of these sections pertain to the inhalation route of exposure.

This chapter concludes by presenting the most recent toxicity reference values available for the substitutes covered in the aerosols sector at the time of publication of this background document (Exhibit 3-1). The list of substitutes presented in Exhibit 3-1 is not all inclusive; however, the Agency believes that the substitutes selected for this review are representative of the types of agents that could replace ODSs in this sector. The Agency has also included in this screen replacement chemicals that may have high toxicity potential to ensure that the assumptions used in the subsequent hazard assessments are valid and conservative.

3.1OCCUPATIONAL[1] (INHALATION) EXPOSURE LIMITS

Allowable occupational exposure limits (OELs) for continuous and short-term exposure, denoted as the workplace guidance level (WGL) and emergency guidance level (EGL), respectively, are used to examine potential risks to workers. Whenever available, the WGLs and EGLs are based on OELs developed by the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), or the American Industrial Hygiene Association (AIHA).

The Occupational Safety and Health Administration (OSHA) is a governmental agency within the Department of Labor that sets enforceable occupational standards. Limits set by OSHA include permissible exposure limits (PELs[2]) and short-term exposure limits (STELs). The PEL is an 8-hour time-weighted average (TWA) airborne exposure limit that is designed, to the extent feasible, to reduce a significant risk of material impairment of health or functional capacity associated with exposure to a hazardous substance. The STEL is the employee's 15-minute TWA exposure that should not be exceeded at any time during a work day. It is designed to protect workers from experiencing adverse acute health effects such as respiratory irritation,

[1] In some cases, these occupational exposure limits were also used to assess general population/consumer risk.

[2] On July 7, 1992, the 11th Circuit Court of Appeals overturned permissible exposure limits (PELs) for 428 chemicals that were set by OSHA in January 1989. Employees are now legally bound to observe the 1971 PELs codified in 29 CFR 1910.100. EPA has, however, decided to continue using the January 1989 proposed PELs for the purposes of the SNAP risk screen because these values are more representative of ACGIH TWA threshold limit values (TLV-TWAs) and AIHA workplace environmental exposure levels (WEELs), and cover a wider range of chemicals.

Exhibit 3-1

Exhibit 3-1 (cont.)

Exhibit 3-1 (cont.)

eye irritation, and narcosis. It must be noted that because OSHA's exposure limits are legally enforceable, OSHA must consider a variety of factors including technologic and economic feasibility in establishing them. Thus, the limits set by OSHA do not solely reflect the toxicological properties of the material.

The National Institute for Occupational Safety and Health (NIOSH), a governmental institute under the jurisdiction of the Department of Health and Human Services, develops recommended exposure limits (RELs) that are non-enforceable. Unlike OSHA, NIOSH is not constrained by issues of technical or economic feasibility or significance of risk when deriving RELs. NIOSH also estimates concentrations of chemicals that are immediately dangerous to life and health (IDLH), which represents "the maximum concentration from which. . . one could escape within 30 minutes . . . without experiencing any escape-impairing (e.g., severe eye irritation) or irreversible health effects" (NIOSH 1990).

The American Conference of Governmental Industrial Hygienists (ACGIH) is a non-governmental limit setting body. ACGIH's non-enforceable TWA threshold limit values (TLV-TWAs) are similar to OSHA's PELs. ACGIH does not formally analyze for technical feasibility, but there appears to be some implicit recognition of feasibility since TLVs are set to be protective for most workers but not so low as to be "unduly restrictive." ACGIH TLVs provided much of the basis for OSHA's 1989 air contaminant standards.

The American Industrial Hygiene Association (AIHA) is also non-governmental. The AIHA workplace environmental exposure levels (WEELs) are like the TLVs in that the justification of a particular WEEL is based predominantly on toxicological information rather than feasibility. However, it is likely that feasibility is considered implicitly since the WEELs are limits that are protective and practical.

The long-term occupational exposure limits (WGLs) used for the SNAP risk screening assessments are based on OSHA PELs, NIOSH RELs, ACGIH TLV-TWAs, or AIHA WEELs, if available. The short-term occupational exposure limits (EGLs) are based on OSHA STELs or NIOSH IDLHs, if available. EPA recognizes that in an industrial setting, OSHA STELs are typically much lower than IDLHs and other emergency guidance levels, and that exposure at the OSHA STEL is not a situation requiring emergency corrective action. Therefore, using OSHA STELs as EGLs is a conservative way to screen risks from short-term exposure to chemicals.

If OSHA, ACGIH, NIOSH, or AIHA OELs were not available for a substitute, and WGLs or EGLs were considered important for the risk screening assessment, they were estimated by EPA. Although the estimated WGLs are intended to be analogous to OSHA PELs, they are different in that PELs are developed by a regulatory process and incorporate complex decision criteria such as technological feasibility. In estimating WGLs, EPA took into consideration the characteristics of workers who are healthier and younger than the general population, and experience intermittent rather than continuous exposure. Where appropriate, WGLs were estimated to be ten times greater than the suggested reference concentration (see Section 3.2.1). If the resulting estimate was greater than the 1,000 ppm TLV-TWA set by ACGIH (1986) ". . . as a guide for good hygiene practice for vapors of low toxicity" (i.e., "good housekeeping" limit), then the latter was used for the risk screening analysis.

The EGL estimate is similar to the NIOSH IDLH (i.e., the maximum concentration from which one could escape within 30 minutes without experiencing escape-impairing or irreversible health effects). It also resembles the emergency exposure guidance level (EEGL) and the short-term public emergency guidance level (SPEGL) suggested by NRC (1986) and the emergency response planning guideline suggested by AIHA (1989). In instances when a substitute has an OEL but the available toxicological data were not sufficient to develop a STEL, the ACGIH excursion limit recommendation, as stated below, was used to estimate the EGL:

"Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work-day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded" (ACGIH, 1992).

Thus, EGLs can range from three to five times the OEL.

In the event of a fire, explosion, or catastrophic emission, the EGL estimates for most of the HCFCs and HFCs and one other chemical in this sector are based on the lowest-observed-adverse-effect level (LOAEL) or on the no-observed-adverse-effect level (NOAEL) for cardiotoxicity in epinephrine-sensitized dogs because the primary concern for acute high-level exposure to these compounds is cardiotoxicity. Cardiac sensitization is of particular interest in these acute, episodic exposures because human heart arrhythmias and sudden death resulting from overexposure to halons, CFCs, and other halogenated hydrocarbons have been documented in workplace settings and in volatile substance abuse (e.g., glue sniffing). As defined by the Agency, cardiotoxicity is the ability of a compound to cause serious and sometimes fatal cardiac arrhythmia, and is best evaluated by exposing the appropriate species, usually the dog, to an agent by inhalation in the presence of epinephrine (Rubenstein and Bellin 1993). The Agency is using these values in the SNAP risk screen to ensure protection of the worker population.

The protocols used to determine the cardiotoxic LOAEL and NOAEL concentrations for each agent are conservative; they entail measurement of cardiotoxic effects in animals made more sensitive to these effects by the administration of epinephrine. The administered doses of epinephrine are just below the concentrations at which epinephrine alone would cause cardiotoxicity in the experimental animal, and are approximately ten times greater than the concentration a human being would likely secrete under stress. Thus, the estimated LOAELs and NOAELs would be conservative for humans even in high-stress situations.

EPA is adopting the OSHA standard (29 CFR 1910, subpart L) section 1910.162 arising from the cardiac sensitization induced by Halon 1301, and is basing its risk assessment decisions for the substitutes that induce cardiotoxicity upon this standard. Under safe use conditions for Halon 1301 (29 CFR 1910.162), the exposure limits, based upon the length of time it takes to evacuate, can be summarized as follows:

- Where egress takes longer than 30 seconds but less than one minute, the employer shall not use the agent in a concentration greater than its LOAEL for cardiotoxicity (e.g., 100,000 ppm for Halon 1301).

- Agent concentrations greater than the LOAEL for cardiotoxicity are only permitted in areas not normally occupied by employees provided that any employee in the area can escape within 30 seconds. The employer shall assure that no unprotected employees enter the area during agent discharge.

- Where egress from an area cannot be accomplished within one minute, the employer shall not use this agent in concentrations exceeding its NOAEL for cardiotoxicity (e.g., 75,000 ppm for Halon 1301).

Under the SNAP risk screen, EPA is only intending to set conditions for the safe use of aerosol substitutes in the workplace until OSHA incorporates specific language addressing gaseous agents into the OSHA regulation. These general conditions will no longer apply once OSHA establishes applicable work place requirements.

3.2GENERAL POPULATION (INHALATION) TOXICITY REFERENCE VALUES

For the aerosols sector, risks to the general population were screened for long-term exposure scenarios. This section discusses EPA's general approach for identifying and developing toxicity reference values applicable to chronic (i.e., lifetime) exposure: verified or interim reference concentrations (RfCs) for noncarcinogens and cancer slope factors (SFs) for carcinogens.

3.2.1Reference Concentrations (RfCs)

When possible, the RfC verified by the Agency's RfD/RfC Work Group, whether or not it has been listed on the Agency's Integrated Risk Information System (IRIS) database, was used to assess the risk from long-term exposure to ODS substitutes in the SNAP background assessments. The RfC is designed to protect the general population against adverse systemic (i.e., noncancer) effects, and is defined as:

"An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3" (EPA 1990).

However, when verified RfCs were not available, interim RfCs were used to evaluate risks associated with chronic exposure to ODS (listed in decreasing order of preference):

·Currently undergoing verification by the Work Group;

·Not yet undergoing verification but contained in the Agency's Health Effects Assessment Summary Tables (HEAST; EPA 1992);

·Estimated from other data for the substitute; or

·Estimated based on surrogate limits.

The remainder of this section discusses the interim RfCs derived from other data for the substitute or estimated based on surrogate limits.

<u>RfCs Estimated From Other Data</u>

In the absence of a verified RfC or an RfC pending verification by the Agency's RfD/RfC Work Group, EPA calculated an interim RfC using the methods specified in EPA's *Interim Methods for Development of Inhalation Reference Concentrations* (EPA 1990). Since adequate human data were not available to calculate RfCs for the proposed substitutes that did not already have RfCs, data obtained in animal inhalation toxicity experiments served as the basis for estimating the RfCs.

If adequate animal inhalation toxicity data were unavailable for a substitute, the interim general population RfC was estimated by extrapolation from oral references doses (RfDs) or oral NOAELs or LOAELs. According to the *Interim Methods for Development of Reference Concentrations*, such route-to-route extrapolation can be performed if pharmacokinetic data, including measurements of absorption efficiency and comparative excretion data (when the associated metabolic pathways are equivalent) are available for both routes of interest, and comparative systemic toxicity data indicate equivalent effects by each route of interest. However, the *Interim Methods* stipulate that oral data should not be used to estimate inhalation exposure limits when the following conditions exist:

(1)When groups of chemicals are expected to have different toxicity by the two routes of exposure (e.g., metals, irritants, and sensitizers);

(2)When a first-pass effect is expected by the liver, or when the pulmonary system was not adequately studied in the oral studies;

(3)When a pulmonary effect is established, but dosimetry comparison cannot be clearly established between the two routes; and

(4)When short-term inhalation studies or *in vitro* studies indicate potential portal-of-entry effects at the lung, but studies themselves are not adequate for RfC development.

The appropriate data to assess these conditions were not available for substitutes requiring route-to-route extrapolation. Therefore, the interim RfCs that were estimated by extrapolation from oral data would most likely be considered "not verifiable" by the Agency's RfD/RfC Work Group. However, in the absence of adequate data and in need of a chronic reference toxicity value for the purpose of the SNAP risk screens, extrapolation from oral data was nevertheless performed according to the following procedures:

(1)Oral RfDs (expressed in mg/kg/day) were converted to inhalation RfCs (expressed in mg/m^3) by multiplying the RfD by the default assumption for average human body weight (70 kg) and dividing by the default assumption for average human breathing rate (20 m^3/day) (EPA 1988).

(2)Alternatively, in the absence of adequate experimental inhalation toxicity data, RfCs for some substitutes were estimated by converting the OEL for that substitute (or a suitable surrogate, as discussed below) to a general population exposure limit. For example, adequate experimental inhalation toxicity data were not available for d-limonene; therefore, the Swedish TLV-TWA (140 mg/m^3 was used. This value is based on an 8-hour TWA worker exposure over a 40-hour work week. To extrapolate to a threshold for long-term continuous general population exposure, the PEL was multiplied by a factor of 10 m^3/20 m^3 (assuming that 10 m^3 are inhaled in an 8-hour day by a healthy worker, extrapolated to 20 m^3 in a 24-hour day by the general population) (Jarabek and Hasselblad 1991), and then divided by an uncertainty factor of 10 to account for sensitive subpopulations.

Interim RfCs Based on Surrogate Limits

For some of the substitutes there are neither RfCs nor adequate experimental inhalation toxicity data, oral RfDs, oral data, or OELs from which to estimate an RfC. In these cases, exposure limits for surrogate chemicals were used. For example, HFC-134a served as the surrogate for HFC-125. Surrogates were chosen by structure-activity relationship (SAR) analysis to provide the worst-case/most conservative estimate for the exposure limit. SAR is used to predict the biological activity of an untested compound based on an examination of analogous chemicals with well-documented health or environmental effects data.

SAR has been an important tool in guiding the development of new chemicals and drugs for many years. EPA has used SAR in assessing new chemicals prior to their manufacture or importation under the Premanufacture Notice Program. Also, the pharmaceutical industry has used SAR to assist in the design and synthesis of new drugs.

3.2.2 Cancer Slope Factors

The cancer slope factor (SF) is used to estimate the upper-bound risk for cancer. Because chemicals that produce cancer are assumed not to show a threshold for their effects, the observed threshold level (i.e., the NOAEL) is not used in the calculation of the cancer SF. Rather, the slope of the dose-response for the effect is used to extrapolate levels at which the risk of the effect is small. It has been argued that the dose-response function for carcinogenicity could be linear and that it is unlikely to exceed linearity in the low-dose region. Thus, the model chosen to extrapolate low-dose effects from the much higher doses at which effects are observed assumes low-dose linearity for cancer production. EPA guidelines (EPA 1987) recommend that, in absence of adequate information to the contrary, the linearized multistage procedure should be used for the extrapolation. This model expresses upper confidence limits on cancer risk as a linear function of dose in the low-dose range. Cancer SFs are estimated by fitting the model to experimental animal carcinogenicity data using the maximum likelihood method. In addition, an upper bound on the dose-response curve is calculated, reflecting uncertainty of extrapolating the curve to low doses at which human exposures are anticipated to occur. This upper bound can be considered to represent the largest reasonable linear extrapolation to low doses consistent with the data. The 95 percent statistical upper limit on the linear term, q_1, is referred to as the q_1*, or the SF.

The SNAP cancer risk estimates were based on cancer SFs that have been verified by EPA's Cancer Risk Assessment Verification Endeavor (CRAVE) Work Group and are contained in IRIS. If these were unavailable, a second choice was SFs that have not yet been verified but are contained in HEAST (EPA 1992). The interim SF for HCFC-22 was estimated using animal data from recently completed chronic inhalation cancer bioassays, according to the methods recommended in the EPA *Risk Assessment Guidelines* (EPA 1987).

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